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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,129	04/11/2005	Satoshi Saito	03419.0023-00	8898

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,129	SAITO ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/7/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks, filed on 7 October 2009.

Claim Status

Claims 1-7 and 16-18 are pending. Claim 8-15 and 19 are cancelled. Claims 1-7 and 16-18 are under current examination. No claim amendments were submitted with the remarks, filed 10/7/2009.

Priority

This application claims benefit as a 371 of PCT/JP03/02833 0 (filed 3/11/2003). This application also claims benefit from the foreign application JAPAN 2002-065880 (filed 03/11/2002). Therefore, the instant application has been granted the benefit date, 3/11/2002, from the foreign application JAPAN 2002-065880.

Formal Matters

In the Action, filed 7/7/2009, the examiner inadvertently made contradictory statements regarding the status of the claims. The applicant requested that the examiner correct this discrepancy. In the Action, filed 7/7/2009, the examiner indicated that the claims were "amended" and that "no amendments were submitted." In fact, on 6/15/2009, the applicant submitted amended claims 1-7 and 16-17. The examiner thanks the applicant for pointing out this discrepancy and apologizes to the applicant for any confusion these comments created.

RESPONSE TO ARGUMENTS

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 16-18 remain rejected under 35 U.S.C. 103(a) as being obvious over Porro et al. (WO99/14335) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive. No amendments were submitted.

The applicant argues that the examiner has not provided a prima facie case of obviousness because his analysis is incomplete. The applicant notes that in the pending rejection, the examiner used MPEP 2143 Rationale "A" (i.e., Combining "Prior Art Element According to Known Methods to Yield Predictable Results). The applicant further suggests that the examiner has not sufficiently articulated elements 3 and 4. MPEP 2143(A) states:

> ***A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results***
>
> To reject a claim based on this rationale, Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
>
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;
>
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
>
> (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

As articulated in the pending rejection and previous actions, the instant claims are directed to a product, namely a bacterial or yeast transformant having a certain

structure. Porro suggests the claimed structure (Finding 1). The art of making recombinant microorganisms is well known and the application of molecular biological techniques to make recombinant microorganisms has been practiced for decades (Finding 2). There is nothing in the state of the art or the applicant's specification that indicates creating a recombinant microorganism having the recited structure would be difficult or unpredictable (Finding 3). Regarding, Finding 4, the Graham factor analysis was articulated by the examiner: the examiner has provided a determination of the scope and contents of Porro et al. (Factor 1); the examiner has Ascertained the differences between the prior art and the claims at issue, namely that Porro et al does not explicitly teach a single embodiment of the claimed transformed bacteria or yeast, but that Porro suggest a transformed yeast having a single integrated copy of a lactate dehydrogenase gene operably linked to a pyruvate decarboxylase promoter (Factor 2); skilled artisans in the art of making transgenic microorganisms typically have a PhD or MD (Factor 3); and the examiner has considered objective evidence present in the application indicating obviousness or nonobviousness, as evidenced by the examiner's responses to arguments (Factor 4). Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant has further argued that "Porro teaches production rate of only lactic acid from lactate dehydrogenase carried on numerous copies of plasmids…one of ordinary skill in the art would not have recognized the increased efficiency of lactic acid production from using integrative vectors in which a single copy of lactate dehydrogenase gene is carried…Hence, one of ordinary skill in the art would not have

recognized any predictability of the results of the proposed combination of features, and the Office has not satisfied the criteria of MPEP 2143(A)(3)" (Remarks, page 3, last paragraph). Porro suggests a transformed yeast having a single integrated copy of a lactate dehydrogenase gene operably linked to a pyruvate decarboxylase promoter; Therefore, a transgenic microorganism having the combination of claimed features is predictable to a skilled artisan. Porro et al. further suggests that a pyruvate decarboxylase promoter is a preferred promoter. As skilled artisan would view the a pyruvate decarboxylase promoter as providing "increased efficiency of lactic acid production." As the specification does not indicate what is meant by "increased efficiency of lactic acid production," (emphasis added by examiner) and "efficiency" is not a claim limitation, the examiner concludes that a skilled artisan would understand that integrating the expression cassette into the genome of the host organism provides advantages (e.g., efficiencies), such as not losing the plasmid during culture. Accordingly, the examiner finds the applicant's arguments unpersuasive.

Accordingly, the examiner hereby maintains the rejection of claims 1-7 and 16-18 under 35 U.S.C. 103(a) as being obvious over Porro et al.

The examiner reiterates the pending rejection:

Claims 1-7 and 16-18 are rejected under 35 U.S.C. 103(a) as being obvious over Porro et al. (WO99/14335).

Claim 1 is directed to a bacterial or yeast transformant into which has been incorporated a DNA for coding a foreign protein having lactate dehydrogenase activity and provided with pyruvic acid substrate affinity that equals or exceeds the pyruvic acid

substrate affinity of the pyruvate decarboxylase inherent in the host organism, wherein a single copy of the DNA for coding the foreign protein has been controllably incorporated such that it is under the control of the genome promoter of the pyruvate decarboxylase gene on the host chromosome, or such that it is under the control of a structural and functional homologue of the genome promoter of the pyruvate decarboxylase gene, which replaces the genome promoter of the pyruvate decarboxylase gene on the host chromosome, and wherein the pyruvate decarboxylase gene on the host chromosome is replaced with the single copy of the DNA for coding the foreign protein having lactate dehydrogenase activity. Porro et al. teach, "yeast strains…transformed with at least one copy of a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences allowing the expression of said gene in yeasts" (page 4, lines 6-11). Porro et al. teach, "yeast strains having…a reduced pyruvate decarboxylase activity and transformed with…a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences" (page 4, lines 12-17). Porro et al. teach any yeast promoter…may be used according to the invention…the promoter of pyruvate decarboxylase gene of K. lactis (KlPDC) is particularly preferred (page 14, lines 18-28). Porro et al. further teach, "Pyruvate decarboxylase gene promoters…are particularly preferred" (page 15, lines 2-5). Porro et al. describe making a triple deletion of the pyruvate decarboxylase genes encoding PDC1, PDC5, and PDC6, using homologous recombination (page 8, lines 25-27). Porro et al. further teach that "PDC genes are highly conserved among different yeast genera" (page 9, lines 7-9). Porro et al. also teach "integrative vectors can be obtained by using homologous

DNA sequences in certain regions of the host genome, allowing, by homologous recombination, integration of the vector" (page 12, lines 12-15).

Claim 2 is directed to the transformant according to claim 1, wherein the foreign protein is a bovine-derived lactate dehydrogenase or its homologue. Porro et al. teach, "the gene coding for lactate dehydrogenase may be of any species (e.g. mammalian, such as bovine)" (page 9, lines 29-30).

Claim 3 is directed to the transformant according to claim 1, wherein the foreign protein is a protein comprised of the amino acid sequence shown in sequence number 1 or its homologue. SEQ ID NO:1 is the bovine lactate dehydrogenase gene. Clearly, Porro et al. contemplates the amino acid encoded this gene or its homologue. Porro et al. teach, "the gene coding for lactate dehydrogenase may be of any species (e.g. mammalian, such as bovine)" (page 9, lines 29-30).

Claim 4 is directed to the transformant according to claim 3, wherein the foreign protein is coded by the DNA sequence shown in SEQ ID NO: 3. Clearly, Porro et al. contemplates this gene or its homologue. Porro et al. teach, "the gene coding for lactate dehydrogenase may be of any species (e.g. mammalian, such as bovine)" (page 9, lines 29-30). SEQ ID NO:3 is a homologue of bovine lactase dehydrogenase which has been codon optimized for expression in Saccharomyces cerevisiae.

Claim 5 is directed to the transformant of claim 4, having the DNA sequence shown in SEQ ID NO:4 as the DNA sequence for coding the foreign protein. SEQ ID NO:4 is the DNA sequence which encodes a homologue of bovine lactase

dehydrogenase which has been codon optimized for expression in Saccharomyces cerevisiae.

Claim 6 is directed to the transformant according to any of claims 1 through 5, wherein the host organism belongs to the Saccharomyces family.

Claim 7 is directed to the transformant according to any of claim 1, wherein the host organism is Saccharomyces cerevisiae. Porro et al. teach transformed yeast, Saccharomyces cerevisiae.

Claim 16 is directed to a transformant of the Saccharomyces family into which a single copy of the DNA for coding a bovine-derived lactate dehydrogenase or its homologue has been controllably incorporated such that the DNA is under the control of a genome promoter of the pyruvate decarboxylase 1 gene on the host chromosome of the Saccharomyces family or such that the DNA is under the control of a structural and functional homologue of the genome promoter of the pyruvate decarboxylase gene, which replaces the genome promoter of the pyruvate decarboxylase 1 gene, and wherein the pyruvate decarboxylase 1 on the host chromosome has been replaced with a single copy of the DNA for coding a bovine-derived lactate dehydrogenase or its homologue. Porro et al. teach, "yeast strains…transformed with at least one copy of a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences allowing the expression of said gene in yeasts" (page 4, lines 6-11). Porro et al. teach, "yeast strains having…a reduced pyruvate decarboxylase activity and transformed with…a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences" (page 4, lines 12-17). Porro et al. teach any yeast promoter…may be used

according to the invention…the promoter of pyruvate decarboxylase gene of K. lactis (KlPDC) is particularly preferred (page 14, lines 18-28). Porro et al. further teach, "Pyruvate decarboxylase gene promoters…are particularly preferred" (page 15, lines 2-5). Porro et al. describe making a triple deletion of the pyruvate decarboxylase genes encoding PDC1, PDC5, and PDC6, using homologous recombination (page 8, lines 25-27). Porro et al. further teach that "PDC genes are highly conserved among different yeast genera" (page 9, lines 7-9). Porro et al. also teach "integrative vectors can be obtained by using homologous DNA sequences in certain regions of the host genome, allowing, by homologous recombination, integration of the vector" (page 12, lines 12-15).

Claim 17 is directed to the transformant according to claim 16, wherein the host is Saccharomyces cerevisiae. Porro et al. teach transformed yeast, Saccharomyces cerevisiae.

Claim 18 is directed to a lactic acid manufacturing method provided with a process for culturing the transformant described in claim 1, and a process for separating lactic acid from the cultured product obtained in the process. Porro et al. teach, "a process for the preparation of…lactic acid by culturing the above described metabolically engineered yeast strains in a fermentation medium containing a carbon source and recovering lactic acid from the fermentation medium" (page 5, lines 5-10).

Porro et al does not explicitly teach a single embodiment of a transformed bacteria or yeast comprising a DNA for coding a foreign protein having lactate dehydrogenase activity operably linked to a functional homologue of the genome

promoter of the pyruvate decarboxylase gene and in which the DNA has been homologously recombined to eliminate the host genome's pyruvate decarboxylase gene. However, Porro et al. teaches all of the structural elements (transformed yeast and bacteria; introduction of a foreign (bovine) lactate dehydrogenase gene; using a pyruvate decarboxylase promoter for expression of exogenous protein expression; and homologous recombination; knocking out the host genome's pyruvate decarboxylase gene). However, Porro et al. does not teach knocking out the host genome's pyruvate decarboxylase gene, by introducing a gene expression cassette in its place.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a single embodiment of a transformed bacteria or yeast comprising a DNA for coding a foreign protein having lactate dehydrogenase activity operably linked to a functional homologue of the genome promoter of the pyruvate decarboxylase gene and in which the DNA has been homologously recombined to eliminate the host genome's pyruvate decarboxylase gene.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (transformed yeast and bacteria; introduction of a foreign (bovine) lactate dehydrogenase gene; using a pyruvate decarboxylase promoter for expression of exogenous protein expression; homologous recombination; knocking out the host

genome's pyruvate decarboxylase gene) are taught by Porro et al. and further they are shown to be used for the production of lactic acid. It would be therefore predictably obvious to use a combination of these elements in a recombinant bacteria or yeast.

In addition, Porro et al. also teach "integrative vectors can be obtained by using homologous DNA sequences in certain regions of the host genome, allowing, by homologous recombination, integration of the vector" (page 12, lines 12-15). A skilled artisan would be guided by the suggestion of Porro to generate a transgenic bacteria or yeast having lactate dehydrogenase integrated into the genome because in his teachings, Porro suggests using vectors capable of homologous recombination to introduce the foreign (bovine) lactate dehydrogenase into the microorganism.

Regarding eliminating the host genome's pyruvate decarboxylase gene by replacing it with a DNA cassette which includes "a DNA for coding a foreign protein having lactate dehydrogenase activity operably linked to a functional homologue of the genome promoter of the pyruvate decarboxylase gene," it would have been obvious because of a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and commonsense. The prior art teaches the need in the art to solve the problem of optimally producing a recombinant microorganism which has been knocked out for a pyruvate decarboxylase gene and further identifies a number of predictable potential solutions for making these deletions/ knockouts (by deletion of the gene; deletion or insertion of selectable markers, point-mutations, frame-shift mutations (Porro, page 10, lines 9-24)). One of ordinary skill in

the art could have pursued the known potential option (of inserting the DNA cassette comprising pyruvate decarboxylase promoter/exogenous lactate dehydrogenase gene) with a reasonable expectation of success. It would be therefore predictably obvious to use a alternative method when eliminating the host genome's pyruvate decarboxylase gene.

Furthermore, codon optimization of the bovine lactate dehydrogenase gene for expression in Saccharomyces cerevisiae is well known in the art and therefore obvious.

Therefore the recombinant bacteria or yeast as taught by Porro et al would have been *prima facie* obvious over the recombinant bacteria or yeast of the instant application.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633